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## Does this patient with AKI need RRT?

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*A 65year old patient is admitted to the ICU 5 days after right upper lobectomy with oliguria (urine output over the past 24h 0.17ml/kg/h =AKI stage 3) and relative hypotension. Serum creatinine has increased from a baseline of 1.36 mg/dL (eGFR 53) to 3.78 mg/dL (AKI stage 2). He has an ileus with vomiting. Antibiotics were commenced 24h earlier because of rising CRP. Postoperative medications included ACE-inhibition and NSAID's. Following ICU admission further fluid resuscitation is commenced as is norepinephrine (0.15microg/kg/min) and the antibiotic spectrum is broadened empirically as the CRP has increased further (505mg/L). Next morning his creatinine has increased to 4.53mg/dl (AKI stage 3), urine output has decreased to 0.1ml/kg/h over the past 12h resulting in a positive fluid balance of 3300ml. Arterial blood gas analysis reveals a pH of 7.39. PaO<sub>2</sub> is 87mmHg, bicarbonate 25meq/L, K<sup>+</sup> 3.9meq/L and urea 128mg/dL He is breathing spontaneously on 2LO<sub>2</sub> with a respiratory rate of 20 breaths/min and chest X-ray shows bilateral basal infiltrates and a limited hydropneumothorax on the lobectomy side.*

Does this patient need RRT? Which factors may guide this decision?

1. Does this patient have an absolute indication for commencing RRT immediately? Generally accepted “classical” indications for urgent RRT include potentially fatal changes in fluid, electrolyte and acid-base balance

and severe azotemia with complications (uremic encephalopathy, pericarditis,...) [1] but agreement on the thresholds for treatment is lacking [2]. None of these indications appear to apply to our patient.

2. Should we wait until the development of classical indications or will commencing RRT earlier improve our patient outcome? Over the past 15 years three small (underpowered) randomized trials [3-5] have addressed this question. No mortality difference was observed but RRT was avoided in 17-37% of the late starters. Moreover, in the most recent trial protocol-driven classical indications were achieved in only one third of the patients in the “late” group; in the other two thirds perceived fluid overload and/or oligoanuria was the main indication for RRT [5]. Observational trials with high risk of residual confounders show conflicting results with one study demonstrating improvement only when RRT is commenced when classical indications are present [6], whereas others observe a higher mortality in patients exhibiting the classical indications on starting RRT, especially when RRT is delayed [7,8]. Several observational studies used retrospective definitions of early and late (based on urea, creatinine, time in ICU, AKI stage, time since AKI stage 3 or degree of fluid overload) which do not inform as to the reason for starting RRT. Mostly a beneficial effect of early start is demonstrated [9]. However, there is a high risk of bias in these studies as none included a control group without RRT and many patients (especially those in the early group) may have received unnecessary RRT. A few recent trials did include a control group without RRT and showed that, even after propensity score matching, the use of RRT increased mortality, especially in less severe forms of AKI [10-11]. It is evident that this study design also has a high risk of residual confounding. Vaara showed lower mortality with pre-emptive RRT in propensity matched analysis but a considerable proportion of patients could not be matched [8].
3. Is sepsis an indication to start RRT earlier? Given that RRT is theoretically capable of clearing inflammatory mediators several authors consider the presence of sepsis as an indication for early RRT. However, this is not substantiated by clinical data. A randomized trial comparing early CVVH

versus standard medical treatment in severe sepsis did actually describe worse outcome in the CVVH group with increased number and severity of organ failures [12]

4. Does RRT help the holistic management of our patients (concept of organ support therapy)? Or does withholding RRT impede us in providing adequate therapy e.g. parenteral nutrition, drugs/antibiotics given potential problems with volume overload complicating AKI? In clinical practice diuretic-resistant oliguria with (established or presumed poorly tolerated) fluid overload and/or large obligatory fluid input is a frequent indication for RRT [2]. Whereas the association between fluid overload and outcome is undoubted, the causative link between both remains to be established. Indeed, a prospective trial on prevention or reversal of fluid overload with early RRT does not exist and it remains even doubtful whether fluid mobilization in the early phase of critical illness is at all feasible. However, in certain subgroups of patients manipulation of fluid balance to prevent fluid overload appears beneficial (stable ARDS, congestive heart failure) [13]. Besides an assessment of the reversibility of kidney dysfunction, the tolerance to fluid overload (mainly cardiac and respiratory acute illness and comorbidity) may therefore become an important factor in the decision to start RRT.
5. It is evident that RRT should not be started if the probability of spontaneous recovery is high. Unfortunately our ability to predict need for RRT in the early stages of AKI is poor although response to loop diuretics may perform better than biomarkers [14]. In clinical practice trends in kidney function and non-renal factors such as severity and potential for short-term reversibility of the underlying disease (e.g. nephrotoxic drugs, low cardiac output due to hypovolemia versus cardiac failure or septic shock) can be very helpful.
6. In the absence of hard data the decision whether or not to start RRT should weigh the harm of unnecessary treatment against the harm of late treatment in the patients that will need RRT. “First do not harm”. The demonstration that AKI is an independent predictor of mortality has fostered the paradigm that earlier initiation of RRT might influence

outcome. AKI indeed has many systemic consequences [15]. However, our current RRT modalities can only correct some them, i.e. electrolyte and acid base disturbance, fluid overload and uremia. In addition, doubling the RRT dose has not been shown to improve outcome and unnecessary RRT is not without harm. RRT (especially intermittent hemodialysis) may cause hypotension that in turn may delay recovery [16]. RRT can result in loss of essential substances (nutrients, drugs...), electrolyte imbalance with potential for arrhythmias, anticoagulation-related bleeding, disequilibrium syndrome, infectious or mechanical complications of the dialysis catheter, bio-incompatibility issues, hypothermia, errors in fluid balance and last but not least costs [17].

7. It is evident that RRT should not be started when further treatment is considered futile [1].

*Premorbidly, our patient was fit and well. Thus starting RRT is appropriate especially as the surgery was potentially curative. He did not present with classical indications and, although oliguric, had normal oxygenation. He has been treated until recently with drugs that potentially impair renal function (NSAIDS, ACEI) and his AKI may be at least partially fluid-responsive (history of ileus and vomiting). RRT was not started. His creatinine further increased to 5.2 on the next day but thereafter decreased steadily.*

In conclusion, hard evidence to guide the optimal timing to start RRT in patients with AKI is lacking resulting in a wide variation in clinical practice. The decision to start RRT should be individualized taking into account not only the severity of AKI and the trend in kidney function but the also the severity and reversibility of the underlying disease, the risk/tolerance of fluid overload and, importantly, the potential harm associated with unnecessary RRT (Table). We can only hope that the two ongoing RCT's [NCT0168259, NCT01932190], with results expected in 2016, will provide more answers to this clinical dilemma.

#### **Compliance with ethical standards**

**Conflict of interest.**

Dr Forni has received honorarium/travel expenses from Fresenius; Astute Medical; Ortho Clinical Diagnostics and Baxter/Gambro/Renal. Dr. Joannidis has received honoraria from Baxter/Renal. There are no other conflicts of interest to report.

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Table. Absolute and relative indications for commencing or not commencing RRT.

<i><b>Reasons to start</b></i>	<i><b>Reasons not to start</b></i>
<b>Absolute</b>	<b>Absolute</b>
Severe hyperkalemia	Futile therapy
Severe acidosis	
Organ dysfunction due to diuretic-resistant fluid overload	
Uremic complications (pericarditis, encephalopathy, ...)	
Life threatening intoxications with substances which can be dialysed (low protein binding (<50%), low volume of distribution and low molecular weight)	
<b>Relative</b>	<b>Relative</b>
Diuretic-resistant fluid overload	Oliguria without clinically important fluid overload
Limited tolerance to fluid overload	Sufficient cardiocirculatory and respiratory reserve to tolerate fluid overload
Rapidly worsening kidney function	Slow deterioration in kidney function
Underlying disease not rapidly reversible	Potential for short term reversibility of the underlying disease
Reduced risk of harm from RRT	Potential harm of RRT (may include unavailability of CRRT)
Furosemide stress test with UO 2h < 200ml	Furosemide stress test with UO 2h >200ml